Kidney International, Vol. 57 (2000), 2634–2643

Analysis of the effect of hemodialysis on peripheral and central arterial pressure waveforms

ADRIAN COVIC, DAVID J.A. GOLDSMITH, LAURA PANAGHIU, MARIA COVIC, and JOHN SEDOR

Renal Medicine, Case Western Reserve University, Cleveland, Ohio, USA; Renal Unit, Parhon Hospital, Iasi, Romania; and Renal Unit, Guy's Hospital, London, England, United Kingdom

Analysis of the effect of hemodialysis on peripheral and central arterial pressure waveforms.

Background. Arterial stiffening is very pronounced in renal patients. Carotid artery stiffening is a powerful predictor of future cardiovascular mortality, and measures of arterial compliance correlate much better with left ventricular mass (LVM) in dialysis patients than does brachial artery blood pressure (BP). The aim of our study was to describe the influence of a hemodialysis (HD) session on arterial cushioning function and to correlate the potential different types of behavior with echocardiographic derived parameters.

Methods. Radial artery pressure waveforms were measured and recorded noninvasively by applanation tonometry in 51 healthy patients on regular three times weekly HD. The data were then converted into aortic pressure waveforms using a regression equation (SphymoCor™ apparatus). Measurements were done pre- and post-HD in order to ascertain the effect of a single HD session on arterial hemodynamics. The augmentation index (AGI; the difference between early and late pressure peaks divided by the pulse pressure amplitude) was used as an index for vascular compliance. Reproducibility was assessed in 20 young healthy subjects by determining the aortic pulse wave augmentation index twice from radial artery BP measurements one minute apart. Intraobserver error was 2.4%. For 10 dialysis patients similarly studied, the intraobserver error was 1.6%.

Results. AGI was correlated with subjects' height ($r = -0.37$, $P = 0.009$), weight ($r = -0.41$, $P = 0.002$), and BP levels: radial systolic BP ($r = 0.33$, $P = 0.018$), radial diastolic BP ($r = 0.29$, $P = 0.036$), and central systolic BP ($r = 0.51$, $P < 0.001$). Comparing the pre- with the post-HD AGI values, four patterns of evolution became apparent: (*1*) The AGI was negative before the HD session and became even more negative afterward ($N = 3$ out of 51). (*2*) The AGI was positive before the HD session but became negative after dialysis ($N = 19$ out of 51). (*3*) The AGI was positive before the HD session and, although diminished afterward, remained positive ($N = 23$ out of 51). (*4*) The AGI was positive before the HD session and increased afterward ($N = 6$ out of 51). We also found that in some patients, AGI remained at lower than predialysis levels for at least 24 hours. Significant relationships between echocardiographic parameters and pulse wave contour (PWC) variables included pre-HD AGI and LVM ($r = 0.47$, $P < 0.001$). There was better correlation between LVM and derived predialysis aortic systolic BP ($r = 0.56$, $P < 0.001$) than measured brachial (peripheral) systolic BP ($r = 0.35$, $P = 0.04$). Patients whose waveform remained abnormal (AGI remained positive) after HD had a more dilated LV (LV-EDD = 52.07 ± 3.48 mm) than did those patients for whom HD restored "normal" arterial hemodynamics (LV-EDD 46.86 ± 4.06 mm, $P < 0.05$).

Conclusions. A standard HD session profoundly affected aortic BP waveform characteristics, with a reduction in wave reflection in 88% of patients. However, restoration by HD of a normal aortic waveform was unusual. Patients whose waveform remained abnormal after HD had larger more dilated LV chambers than did those patients for whom HD restored "normal" arterial hemodynamics.

Key words: dialysis, arterial stiffening, cardiovascular mortality, left ventrical mass, hemodynamics, blood pressure.

Received for publication July 13, 1999
and in revised form October 20, 1999
Accepted for publication January 21, 2000

Arterial hypertension is common in renal disease and is linked to survival on dialysis in some series [1, 2]. The reasons for hypertension are diverse, including salt and water overload and also factors that operate independently of volume status [3]. Blood pressure (BP) levels, especially when measured using ambulatory BP monitoring [4], are linked to left ventricular mass (LVM) in dialysis patients [5], and LVM increase has an unfavorable effect on dialysis patient survival [6].

Blood pressure recordings are virtually always taken using the brachial artery, and brachial artery determinations are thought accurately to reflect BP throughout the arterial circulation. While mean BPs are indeed similar in different regional circulations, the systolic and diastolic BPs vary considerably [7]. Pulse pressure is lowest in healthy subjects in the proximal aorta and increases progressively as more distal parts of the circulation are reached [7, 8]. The interaction between incident and retrograde (from small arterial branch sites) arterial wave energy represents the major explanation of the previously mentioned variability. The physical location in the arterial tree of the summation point of these energies is dependent in health on arterial length (closely coupled to patient height), to arterial stiffness, and to

wave-energy reflectance characteristics. The changes seen in pulse-wave contour with increasing age and in disease states, such as hypertension and renal failure, arise from increased arterial stiffness (faster pulse-wave velocity) and increased energy reflection (small vessel pathology) [9, 10]. This process of arterial stiffening is very pronounced in renal patients [reviewed in 11]. Carotid artery stiffening is a powerful predictor of future cardiovascular mortality [12]. Measures of arterial compliance correlate much better with LV mass in dialysis patients than does brachial artery BP [13]. The reasons for the significant loss of arterial elasticity in renal disease are poorly understood, but may result from dyslipidemia, excess endothelin [14], and excessive vessel calcification [15].

In health, hypertension and renal disease, arterial distensibility can be influenced favorably and unfavorably by drugs [16, 17], even at doses that do not cause a measurable change in brachial artery BP. Angiotensin-converting enzyme (ACE) inhibitors have the greatest potential of all antihypertensives to induce a reduction in LV mass per mm Hg BP reduction in essential hypertensives [18], are one of very few interventions that can reduce LV mass in dialysis patients [17], and have profoundly beneficial effects on arterial hemodynamics and wave energy reflection [19].

The fact that even in dialysis patients with severe loss of arterial cushioning function there can be—with appropriate drug therapy—a rapid and sustained improvement in arterial function [11] prompted us to investigate whether a hemodialysis (HD) session, during which both the blood volume and the vasoactive hormonal profile change, would influence arterial hemodynamics. We chose to use a new apparatus, validated in health and in many disease states, to allow for rapid, accurate and reproducible measurement and analysis of peripheral arterial waveforms, in order to derive proximal aortic waveforms, indices of reflected wave energy, and cardiac functional parameters [20–22].

METHODS

Study population

The study took place over a three-month period in a single regional renal unit northeast of Romania. Fifty-one stable chronic HD patients, all on dialysis for more than three months, were enrolled for the study. Exclusion criteria were regular cardiovascular instability on dialysis (symptomatic dialysis hypotension requiring saline infusion occurring in greater than 5% of dialysis sessions over the preceding half year), major comorbid conditions (for example, malignancy), recent (within three months) myocardial infarction or unstable angina, a history of congestive cardiac failure, evidence of peripheral vascular disease, recent (within three months) transient ischemic attacks/cerebrovascular accidents, and diabetes mellitus. All 120 patients on the unit were subjected to echocardiography for clinical reasons, and about 25 were identified as being non-"echogenic." From the remaining 95 patients, 74 fulfilled the other inclusion criteria. Fifty-one were invited to participate and were able to complete the study successfully.

Table 1. Demographic data for the full cohort of 51 patients included in this study

	Mean ± SD	Median	Min	Max
Age *years*	41.3 ± 10.7	42.0	20	61
Gender *M/F*	28/23			
Weight *kg*	65.7 ± 13.5	66.2	21.2	99.0
Height *cm*	166.5 ± 7.7	167.0	151	181
Time on dialysis *months*	49.7 ± 27.7	41.0	12	121
Kt/V	1.34 ± 0.23	1.3	1.1	1.5
Hematocrit[a] %	29.5 ± 6.6	28	22	46
Plasma total protein *g/L*	7.1 ± 0.7	7.2	5.5	9.6

Kt/V, urea kinetic modeling.
[a]11 patients on EPO

Dialysis protocol

Dialysis was performed three times weekly using five-hour treatments using Fresenius 4008E machines, blood access by means of mature radial arteriovenous (AV) fistulae, blood flow rates at 300 to 350 mL/min, dialysate flow rates at 500 mL/min, and bath conductivity 135 mS, bath calcium 1.75 mmol/L, bath buffer bicarbonate. Diet comprised 50 mmol/L sodium and 1.2 g high-grade protein per day. Fluid allowance was 750 mL per day. Antihypertensive drugs were only employed if salt and water restriction and extended dialysis sessions failed to bring predialysis BP lower than 150/90 mm Hg. All antihypertensives were discontinued for 48 hours before the study dialysis sessions. No exogenous saline or other plasma expanders were used in the study dialysis sessions. The study dialysis session in all cases was the second midweek dialysis (Wednesday or Thursday session). Baseline demographic, clinical, and laboratory parameters are shown in Table 1.

Measurements

Brachial artery BP was measured in all subjects in the nonfistula arm, after 10 minutes of supine rest, using a standard sphygmomanometer with a cuff circumference appropriate to the arm width (phase V Korotkoff sound for diastolic BP) and was calculated as the mean of two readings one minute apart. BP was measured 10 minutes before connection to and 15 minutes after disconnection from the dialysis machine.

Using the SphygmoCor™ pulse wave velocity apparatus (PWV Inc., Sydney, Australia), a Millar arterial pressure tonometer, and pulse wave analysis software package (PWV Inc.), radial arterial waveform in the nonfistula arm was measured by applanation tonometry [20–22]. Briefly, with the arm carefully supported in an anatomi-

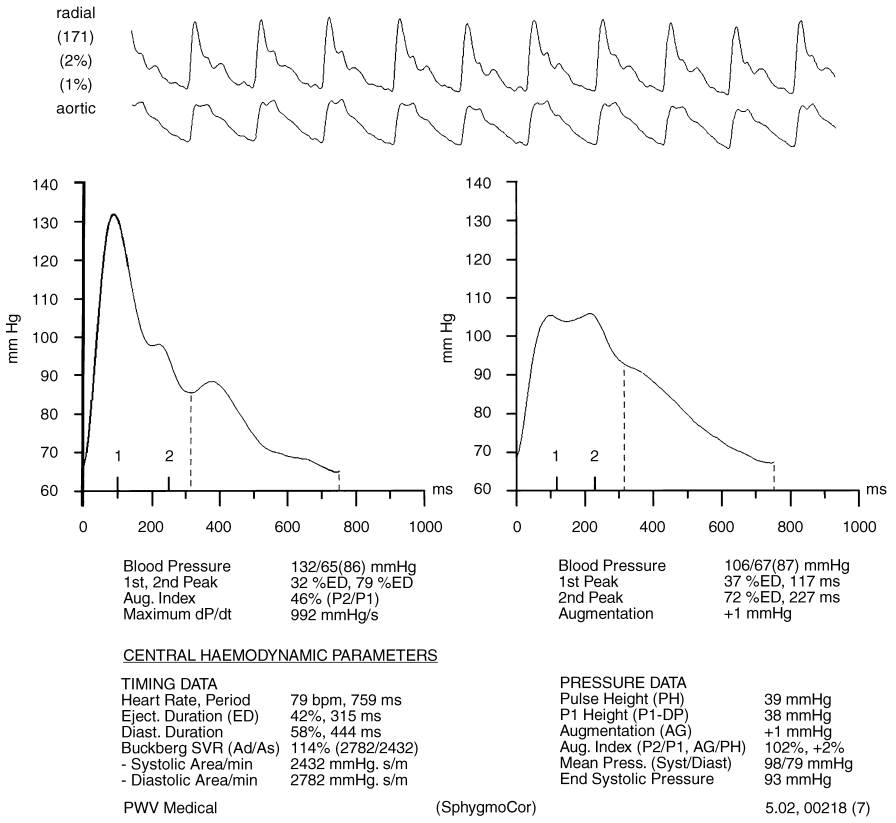

Fig. 1. Representative pulse waveform from a subject with normal brachial artery blood pressure (BP) levels, and virtually normal aortic function (AGI of +2%). Note the difference between the aortic and the radial BP values and the waveforms.

cally neutral position and the wrist extended by about 10 degrees, a tonometer probe was pressed against the radial artery as it passed over the head of the radius. Real time pulse arterial waveform was displayed on a laptop computer screen, and the signal intensity and quality maximized by careful repositioning of the probe. Built-in quality-control measures included achieving signal amplitude of 100 arbitrary units and having <5% variance in both the pulse waveform beat-to-beat maximum amplitude and the diastolic energy waveform characteristics. Thirty seconds of suitable quality cardiac cycles (typically 40 cycles) were recorded and averaged by the software. From this averaged composite radial waveform ejection duration, diastolic duration, first and second systolic pressure peak, radial artery augmentation index (discussed later in this article), and maximum rate of increase in BP in systole were derived.

The software analytical program also derived in real time from the measured radial artery waveform an aortic BP waveform using a validated transfer function algorithm [23, 24]. From the derived aortic BP waveform, the ejection duration, diastolic duration, first and second systolic pressure peak, and aortic augmentation index (discussed later in this article) were also calculated as described previously (Figures 1 and 2 show the typical radial and derived aortic arterial waveform traces used in this study).

One key parameter derived from this waveform analysis was the arterial augmentation index, which is calculated as the systolic BP peak 2 minus systolic BP peak 1 divided by pulse pressure (systolic BP − diastolic BP; Figs. 1 and 2). Compliant vessels, such as the aorta in young healthy adults, generally result in negative augmentation. As arterial stiffness increases and the rate of antegrade energy propagation increases, augmentation becomes positive. This is accentuated if more energy is reflected back from peripheral arterial branching points (increased reflection coefficient), and the timing of the reflected energy wave is also affected by the rate of propagation (increased with increased arterial stiffness). Thus, AGI is a parameter that is determined by arterial pulse wave velocity and by wave reflection properties.

These measurements were taken by a single observer, each over a minute and in duplicate, 10 minutes before and 15 minutes after the standard HD study session. The same observer repeated the pulse waveform analysis 24 and 48 hours after the index dialysis session, in the absence of the administration of any antihypertensive drugs for that period.

Echocardiography

Starting 10 to 14 hours after the end of the study dialysis session, each patient underwent echocardiography study (Toshiba SSA-340A echocardiography machine; Toshiba

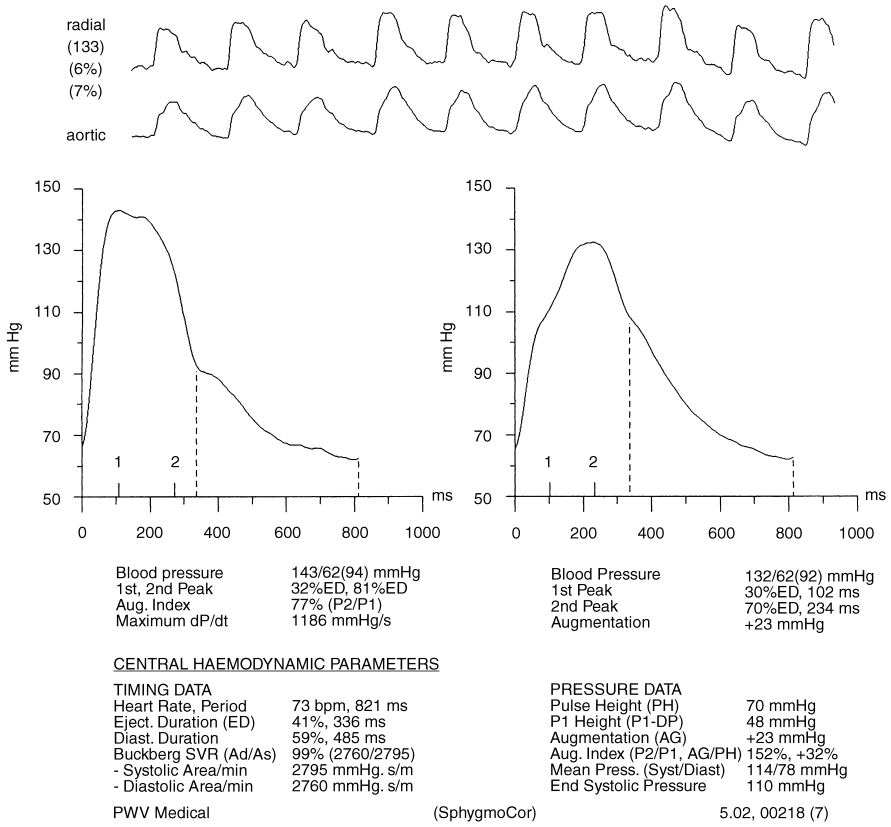

Fig. 2. Representative pulse waveform from a subject showing raised brachial artery BP levels and abnormal aortic function (AGI of +31%). Note the greater similarity between the aortic and radial BP values and waveforms compared with Figure 1.

Corporation, Tokyo, Japan) and venesection for determination of hematocrit, ionized plasma calcium, plasma phosphate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and plasma albumin.

Echocardiography was performed and videotaped, and the following parameters were determined: LV interventricular septum thickness (IVST), posterior wall thickness (PWT), end-systolic diameter (ESD), end-diastolic diameter (EDD), left atrial diameter (LA), fractional shortening index (FSI), and mean velocity of circumferential fiber shortening (MVCF). LV ejection time, LV end-systolic BP, and LV end-systolic wall tension were also measured or derived. Wall and chamber measurements were normalized for body surface area to derive LVM index (LVMI). Analyses were performed by two independent technicians who were blinded to patient information, and using videotape from the echocardiography sessions.

Statistics

Intergroup PWC, BP data, and echo data were compared by two-tailed nonpaired *t*-tests. Significant differences in proportions were assessed by the chi-square test. One-way analysis of variance was used for multiple comparisons of the AGI change with time, following the HD session. Stepwise multiple linear regression analysis was performed using the augmentation index as the dependent variable. Two-tailed $P < 0.05$ was considered significant.

RESULTS

Study population

Selected demographic, clinical, and laboratory characteristics of the study group are presented in Table 1. The group average BP before the study dialysis session was systolic BP 140.9 ± 21.2 over diastolic BP 91.0 ± 14.6 mm Hg. With antihypertensive medication being stopped for 48 hours (one interdialytic interval) before the study, 20 patients had values greater than 140 mm Hg systolic BP or 90 mm Hg diastolic BP at the time of the study. Nineteen patients were regularly taking antihypertensive medication (11 patients treated with 1 drug, 7 patients by a combination of two drugs, and 1 required a combination of three drugs). Antihypertensive regimens had not been changed for the last six months. All patient were normotensive (that is, averaged predialysis BP values less than 140/90 mm Hg) when taking medication for the previous three months.

The main predialysis PWC parameters for the entire population are presented in Table 2.

Table 2. Details of derived aortic pulse pressure (PH), augmentation (AG), the ratio of the second to the first systolic waveform peaks (P2/P1) and the derived parameter, augmentation index (AGI) using pulse wave contour analysis from applanation tonometry of the radial artery for the full cohort of 51 patients included in the study

	Mean ± SD	Min	Max
PH	41.35 ± 13.56	15	73
AG	9.95 ± 7.96	−5.3	27.5
P2/P1	132.9 ± 25.7	85.5	183.5
AGI = AG/PH	21.48 ± 13.90	−15	43.5

Abbreviations are: PH, pulse pressure height; AG, augmentation; P2, second systolic pulse peak; P1, first systolic pulse peak; P2/P1, ratio of P2 to P1.

Table 3. Determinants of the augmentation index

Parameter	*P*	*r*
Univariate regression		
Height	=0.011	=−0.35
Weight pre-HD	=0.003	=−0.42
Brachial (peripheral)-SBP	=0.018	=0.33
Brachial (peripheral)-DBP	=0.036	=0.29
LV ejection time	=0.003	=0.41
LV end systolic pressure	<0.001	=0.49
LV period, heart rate derived	<0.001	=0.59
LVM	<0.001	=0.47
EDD	<0.001	=0.68
ESD	<0.001	=0.64
SV (stroke volume)	<0.001	=0.58
LV wall stress	<0.001	=0.44
Multiple regression analysis		
End systolic LV wall stress, $P = 0.055$, t = 1.97, beta = 0.63;		
LVET period, $P = 0.0069$, t = 2.85, beta = 0.25;		
LV − EDD, $P = 0.023$, t = 2.36, beta = 0.41		

AGI is defined in Table 2 for the full cohort of 51 patients included in the study. Linear regression analysis and multiple regression analysis used the augmentation index as the independent variable.

Coefficients of variability for SphygmoCor™-derived parameters

In 20 young healthy volunteers, aortic pulse wave augmentation index was derived twice from radial artery BP measurements one minute apart. Intraobserver error was 2.4%. For 10 dialysis patients similarly studied, the intraobserver error was 1.6%, which was in keeping with previous reports [22]. Also, a subgroup of six dialysis patients was studied twice by one observer while they were hospitalized, but with a gap of four hours between readings, at rest and without dialysis or hemodynamic drugs, in order to assess intraobserver reproducibility. The intraobserver error was 5.2%. Finally, when two SphygmoCor™ operators measured aortic pulse wave augmentation index in the 20 healthy subjects, again at one minute apart, the calculated interobserver error was 3.5%.

Factors influencing AGI as an index of aortic compliance

Although on univariate analysis the augmentation index was significantly related to patients' anthropometric data, BP levels and cardiac echocardiographic parameters, the only relevant determinants were the LV internal diameter, LV wall stress, and the heart period by multiple regression statistical analysis (Table 3).

Influence of the hemodialysis session on AGI

Comparing the pre- with the post-HD AGI values, four patterns of evolution became apparent: (*1*) In one group the AGI was negative before the HD session and became even more negative afterwards ($N = 3$ out of 51 patients). (*2*) In the second group, the AGI was positive before the HD session but became negative after dialysis patients ($N = 19$ out of 51). (*3*) In a third group the AGI was positive before the HD session and, although diminished afterward, it remained positive ($N = 23$ out of 51). (*4*) Finally, the AGI was positive before the HD session and increased afterward in 6 out of 51 patients. The magnitude of change in AGI following the dialysis session, as expressed as the percentage of the baseline value, was related to BP levels before HD (systolic BP, $P = 0.002$, $r = 0.41$; diastolic BP, $P < 0.001$, $r = 0.45$) and to the magnitude of fluid removal (of weight loss, $P = 0.037$, $r = 0.30$). There was no relationship with the change in heart rate, hydration status, as assessed indirectly by inferior vena cava (IVC) diameters pre- and post-HD, or changes in electrolytes (Ca^{++}, K^{+}, PO_4^{3-}, and Na^{+}).

Considering that a negative AGI best approximates a compliant pulse wave (Figs. 1 and 2), we further analyzed two subpopulations: Cohort A in which dialysis restored/maintained the normal pattern (that is, negative augmentation) of the aortic pulse waveform (groups 1 and 2 above); and cohort B in which a positive AGI was recorded both before and after the dialysis session (groups 3 and 4). Cohorts A and B were also significantly distinct when evaluating the amplitude of change in AGI, expressed as a percentage of the initial predialysis value (Fig. 3). Demographic, biochemical, treatment, and echocardiographic differences between cohorts A and B are shown in Tables 4 and 5, with additional information given on the small group of patients (group 4), in which the aortic augmentation index was increased immediately after dialysis compared with predialysis values. Patients with an abnormal (persistently positive) postdialytic pattern of vascular compliance had significantly larger hearts, although the systolic function was almost identical. LV wall thickness was also similar between cohorts A and B.

Figure 4 shows the evolution of change in pulse waveform characteristics in the subsequent 48-hour interdialytic interval. AGI values around an index dialysis session for the cohort A subjects were 14.3 ± 14.7 at −10 minutes, −15.3 ± −10.6 at 15 minutes ($P < 0.001$), 2.4 ± −12.3 at 24 hours ($P < 0.05$), and 15.2 ± −9.6 (P = NS) at 48 hours. Similarly timed AGI values for the cohort

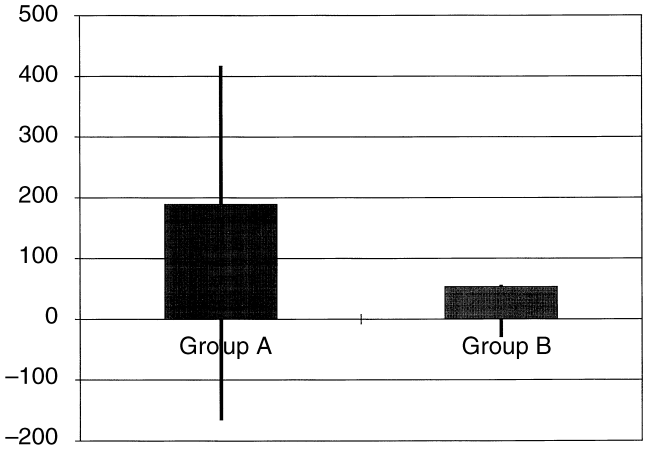

Fig. 3. Changes in the augmentation index (AGI) following the hemodialysis (HD) session. Subjects regaining a normal waveform profile post-HD (cohort A) had a significantly greater amplitude of change in AGI ($P < 0.005$) than did subjects with a persistent abnormal profile (cohort B). Changes in AGI are expressed as the % change from the baseline pre-HD corresponding AGI value.

B subjects were 26.9 ± 10.6 at −10 minutes, 16.0 ± −8.4 at 15 minutes ($P < 0.05$), 24.3 ± −11.2 at 24 hours (P = NS), and 27.2 ± −10.8 at 48 hours (P = NS). In contrast to the marked aortic pulse waveform differences between the cohorts of subjects in the interdialytic interval of 48 hours (Fig. 4), we found that at each time point, there was no statistically significant difference between measured brachial artery systolic and diastolic BP values between cohort A and cohort B subjects.

Significant relationships between echocardiographic parameters and PWV variables have been described in the section dealing with AGI determinants (Fig. 5 shows the relationship between pre-HD AGI and LVM, $r = 0.47$, $P < 0.001$). There was better correlation between LV mass and derived predialysis aortic systolic BP ($r = 0.56$, $P < 0.001$) than measured brachial (peripheral) systolic BP ($r = 0.35$, $P = 0.04$).

DISCUSSION

Pulse waveform energy contour analysis, formerly only of historic interest [25], is now increasingly used as a technique to investigate large arterial cushioning function and wave reflected energy. When the pulse waveform information can be obtained rapidly and noninvasively, this becomes a powerful tool to investigate the cardiovascular response to different disease states and drugs.

Previous reports have shown marked abnormality of arterial compliance in dialysis patients [26], the underlying reasons for which are uncertain. Acute (after one dose) and chronic (after months of therapy) improvements in these parameters can be induced using ACE inhibitors in hypertensive [27] and dialysis [17] patients. Factors in renal disease and dialysis that could impinge on arterial structure and function include atherosclerosis and arteriosclerosis [28], vessel calcification [15] dyslipidemia [14], high circulating endothelin levels [14], dysautonomia [29, 30], and chronic salt/water overload [31]. Certainly, it has been shown that endothelial function is measurably improved by HD in a way that is consistent with the removal of circulating inhibitors of nitric oxide synthase [32].

Our study demonstrated that despite adequate brachial artery BP control, there were significant abnormalities of arterial cushioning function (as reflected by the AGI) in this dialysis cohort. Moreover, it was not possible to predict aortic hemodynamic responses following a dialysis session from brachial artery BP measurements. This confirms other investigators' findings using a similar methodological approach. Saba et al used the same cutoff value, that is, an AGI of zero to differentiate between normal compliance function (AGI < zero) and reduced compliance function (AGI > zero) [33]. Using this criterion, 95% of our dialysis cohort had abnormal arterial behavior before HD, and 55% retained that abnormality after HD. Overall, in 88% of cases, there was some improvement in arterial hemodynamics as a result of HD.

From our results, we hypothesize that dialysis improves vascular compliance by removing vasoconstricting factors or by inducing the elaboration of vasodilating factors. The difference in the amplitude of the AGI change pre- versus post-HD might be explained by the presence of profound vascular structural damage (vascular calcifications) in the 55% of the subjects who still retain an abnormal compliance profile after the dialysis session. Possible alternative explanations were also considered but thought unconvincing, including the physicochemical properties of the arterial tree and blood circulation. Thus, a shorter cardiac cycle as a result of tachycardia induced by dialysis may dramatically change the pattern of the waveforms, but all the subjects were studied 15 minutes after disconnection from the dialysis machines, and the recorded difference in pulse rates before and after dialysis were not large enough to have a significant impact on augmentation. Also, a reduction in large arterial diameter by ultrafiltration—analogous to left heart cavity volume changes—returning the degree of stretch of the arterial wall to a more favorable part of the stretch-tension hysteresis curve may have an impact on arterial-cushioning function, although we could show no relationship with IVC diameter or with ultrafiltration volume. The reduction in BP after dialysis, which though present, was small and again not related to the degree of improvement in augmentation was not likely to be an important confounding factor, especially when one considers the remarkable dissociation between aortic pulse waveform characteristics and brachial BP levels in the interdialytic interval, where a marked difference in evolution of AGI

Table 4. Comparison between patients with different patterns of change in aortic pulse waveform profile following the hemodialysis session: Demographic, biochemical, treatment and blood pressure data

	Cohort A ($N = 22$)	Cohort B ($N = 29$)	Group D ($N = 6$)
Demographic parameters			
M/F	15/7	13/16	3/3
Age *years*	40.1 ± 11.1	42.3 ± 10.5	40.8 ± 6.9
Weight *kg*	71.2 ± 13.5	61.4 ± 12.0[a]	65.6 ± 19.5
Height *cm*	169.8 ± 7.7	163.9 ± 6.8[a]	163.7 ± 7.6[a]
BSA m^2	1.819 ± 0.200	1.676 ± 0.188[a]	1.762 ± 0.270
Dialysis parameters			
Time on dialysis *months*	45.7 ± 28.0	52.7 ± 27.5	56.2 ± 19.5
Kt/V	1.35 ± 2.1	1.33 ± 1.9	1.38 ± 0.8
Weight loss			
kg	3.0 ± 1.1	2.6 ± 1.2	2.7 ± 1.93
% pre-HD weight	4.3 ± 1.2	4.1 ± 1.5	3.85 ± 1.67
Conductivity *mS*	139.2 ± 2.2	140.0 ± 2.5	139.0 ± 3.74
Hematocrit %	30.1 ± 7.2	29.1 ± 6.1	31.5 ± 4.5
Total protein *g/L*	6.93 ± 0.68	7.20 ± 0.75	7.16 ± 0.75
Blood pressure data			
Radial pre-HD SBP/DBP *mm Hg*	141.7 ± 21.7/88.9 ± 16.6	138.8 ± 22.3/83.4 ± 13.3	124.6 ± 22.3/78.4 ± 10.3
Central pre-HD SBP/DBP *mm Hg*	126.9 ± 22.0/88.5 ± 13.9	128.9 ± 22.0/85.3 ± 13.8	113.2 ± 18.5/77.8 ± 10.4
Radial post-HD SBP/DBP *mm Hg*	125.0 ± 25.7/74.6 ± 12.2	130.4 ± 24.3/78.8 ± 13.2	118.8 ± 33.3/75.8 ± 9.2[b]
Central post-HD SBP/DBP *mm Hg*	105.1 ± 19.6/76.6 ± 12.6	117.3 ± 21.8/80.1 ± 13.8[a]	108.4 ± 29.7/74.7 ± 18.9
Antihypertensives			
% patients	40.9	34.5	30
% patients on >1 drug	22.7	10.3	30
% patients on ACE-I	36.4	10.3[a]	16.6

Abbreviations are: BSA, body surface area; Kt/V, derived Kt/V (urea); LV, left ventricle; EDD, end-diastolic LV diameter; ESD, end-systolic LV diameter; IVST, interventricular septal thickness; PWT, LV posterior wall thickness; EDD/PWT, asymmetrical hypertrophy measurement; LVM, LV mass; LVMI, LV mass indexed for BSA; FSI, fractional shortening index; MVCF, mean velocity of circumferential fiber shortening; ESP-End systolic press, end-systolic LV pressure; ESP/PWT, measure of LV wall tension; IVC, inferior vena cava (width).

Cohort A is defined as patients in whom dialysis restores a normal aortic pulse waveform pattern; Cohort B comprise patients with a persistent abnormal aortic pulse waveform pattern following dialysis.

Group D is a subgroup of patients in which the AGI increases following the hemodialysis session.

[a]Significant difference ($P < 0.05$) from corresponding cohort A value

[b]Significant difference ($P < 0.05$) from corresponding cohort B value

Table 5. Comparison between patients with different patterns of change in aortic pulse waveform profile following the hemodialysis session: Echocardiographic evaluation

	Cohort A ($N = 22$)	Cohort B ($N = 29$)	Group D ($N = 6$)
EDD *mm*	46.88 ± 4.06	52.07 ± 3.48[a]	53.8 ± 1.5[a]
ESD *mm*	31.23 ± 3.63	34.5 ± 2.95[a]	33.9 ± 1.6[a]
IVST *mm*	12.05 ± 1.17	11.55 ± 1.21	11.50 ± 1.37
PWT *mm*	11.95 ± 1.25	11.86 ± 1.26	11.81 ± 1.47
EDD/PWT	3.95 ± 0.48	4.43 ± 0.51[a]	4.6 ± 0.53[a]
LVM *g*	252.01 ± 54.09	289.27 ± 55.14[a]	303.1 ± 50.9[a]
LVMI g/m^2	139.87 ± 33.9	174.40 ± 38.64[a]	176.9 ± 47.5[a]
FSI %	33.45± 3.23	33.7 ± 3.89	37.1 ± 2.75[a,b]
MVCF *%/ms*	0.116 ± 0.019	0.110 ± 0.016	0.128 ± 0.013
End systolic press *mm Hg*	115.19 ± 19.0	116.26 ± 19.17	103.75 ± 15.6
ESP/PWT *mm Hg/mm*	9.703 ± 1.679	9.866 ± 1.736	8.814 ± 1.34
Ejection duration *ms*	294.9 ± 54.9	309.02 ± 29.3	291.6 ± 44.6
Stroke volume *mL*	63.3 ± 11.5	80.9 ± 13.9[a]	93.2 ± 8.2[a,b]
IVC *mm*	18.9 ± 3.4	19.4 ± 4.1	19.8 ± 2.5

Abbreviations are: BSA, body surface area; Kt/V, derived Kt/V (urea); LV, left ventricle; EDD, end-diastolic LV diameter; ESD, end-systolic LV diameter; IVST, interventricular septal thickness; PWT, LV posterior wall thickness; EDD/PWT, asymmetrical hypertrophy measurement; LVM, LV mass; LVMI, LV mass indexed for BSA; FSI, fractional shortening index; MVCF, mean velocity of circumferential fiber shortening; ESP-end systolic press, end-systolic LV pressure; ESP/PWT, measure of LV wall tension; IVC, inferior vena cava (width).

Cohort A is defined as patients in whom dialysis restores the normal aortic pulse waveform pattern; Cohort B comprises patients with a persistent abnormal aortic pulse waveform pattern following dialysis.

Group D is the subgroup of patients in which the AGI increases following the hemodialysis session.

[a]Significant difference ($P < 0.05$) from corresponding cohort A value

[b]Significant difference ($P < 0.05$) from corresponding cohort B value

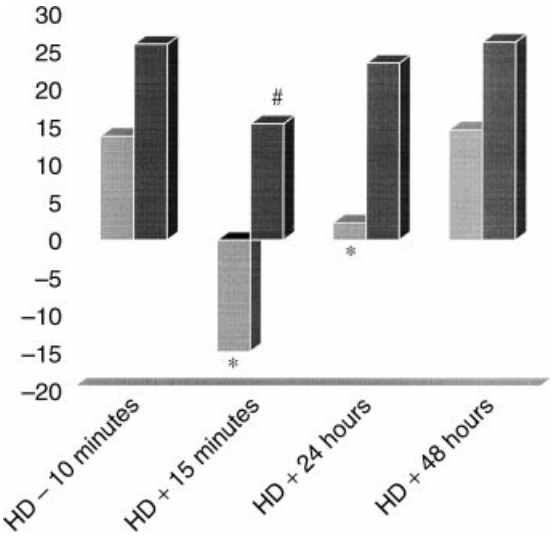

Fig. 4. Evolution of AGI in the interdialytic interval. Subjects from cohort A (those whose aortic augmentation index was restored to normal by HD) showed a much greater change in aortic AGI comparing values 10 minutes before HD to 15 minutes after HD. Moreover, the normalization of the aortic waveform was evident even 24 hours after dialysis, whereas subjects from cohort B, in which HD did not restore normal aortic waveforms, not only started from a higher (that is, more abnormal) aortic AGI, but the small change brought about by HD was lost at 24 hours, where aortic AGI values were the same as predialysis AGI values. For both cohorts, aortic AGI values were very similar to predialysis levels 48 hours later, that is, just before the next dialysis session. #Cohort B AGI significantly different compared with pre-HD values (one-way ANOVA). **Cohort A AGI significantly different compared with pre-HD values (one-way ANOVA).

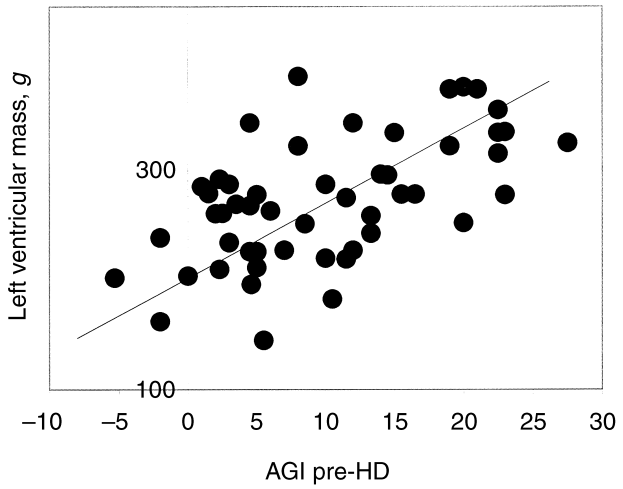

Fig. 5. Relationship between AGI and LVM. This figure shows the close relationship ($r = 0.47$, $P < 0.001$) between echocardiographically measured LV mass and the value of the aortic augmentation index measured just before dialysis.

with time was seen between the more "reactive" cohort A patients and the less "reactive" cohort B patients (Fig. 4), while brachial BP values were similar comparing these two cohorts over that same interdialytic interval. Finally, altered cardiac inotropism following the dialysis session was excluded, as there was no baseline echocardiographic demonstration of poor systolic LV function and no consistent change pre- to postdialysis of the initial rate of rise of BP in the first part of cardiac systole after aortic valve opening (dP/dt; data not shown).

There is likely to be a complex interplay between both functional and structural components of increased arterial stiffness and factors determining the speed and extent of reflected wave energy in the circulation. Angiotensin-converting enzyme (ACE) inhibitors in previous studies have been to shown to reduce wave reflection [17], and clearly, the greater proportional use of ACE inhibitors in the more favorable cohort we describe may have contributed to this observation. Our study was not designed to find the explanation for these phenomena, but clearly, these and other possible mechanisms can be investigated in future studies. Using a more sophisticated version of the SphygmoCor™ apparatus, it is possible to measure aortic pulse wave velocity as well as aortic augmentation index directly. Thus, an attempt could be made to determine whether the dialysis-induced alteration in AGI that we describe comes about because of decreased arterial stiffness (increased arterial compliance) or because of a change in the wave energy reflection coefficient (both of which determine AGI).

Our data reveal a much closer relationship between derived aortic, rather than measured brachial, predialysis systolic BP and LV mass ($r = 0.56$, $P < 0.001$, compare $r = 0.35$, $P = 0.04$). London et al showed that aortic pulse wave velocity was able to explain much more of the variance in LVM than could brachial BP [11]. More important, we have also showed that subjects whose augmentation index remained positive (that is, abnormal) even after dialysis (cohort B; **Results** section) had larger hearts than those subjects whose augmentation index "normalized" with dialysis (cohort A). As shown in Figure 4, these cohort B subjects with the highest augmentation indices, in whom HD was not able to restore hemodynamics to normal, returned to their predialysis AGI values before 24 hours after HD, compared with the normalized cohort A, in whom the 24-hour postdialysis augmentation index was still significantly lower than the predialysis augmentation index. In this context, LV wall stress would be higher for a longer period of time in the cohort B subjects, and this may explain their tendency for greater LV mass. It is also of interest that significantly fewer patients in this less favorable cohort B cohort (higher predialysis AGI, less reduction with HD, greater LVM) were on ACE inhibitors, and that patients in this cohort were significantly shorter of stature (lack of height meaning that the pulse wave has less distance to travel to and from the proximal aorta, which for any given aortic pulse wave velocity would mean earlier/greater wave reflection in shorter patients). Patients with higher

AGI have more dilated left ventricles with a higher wall stress and a lower heart rate.

Using portable noninvasive apparatus (such as the SphygmoCor™) to record and analyze pulse wave energy predialysis and postdialysis may facilitate the discovery of a distinct subgroup of patients at high risk for LV dilation and ultimately heart failure, but prospective confirmation is required. Moreover, this might be a tool for establishing a more effective use of antihypertensives (with preliminary data supporting a case for an extended use of ACE-inhibitors in patients with stiff arteries) and a more refined control of HD sessions. Nevertheless, the genesis of increased arterial stiffness, increased arterial pulse wave velocity, and increased wave energy reflection, assayed as increased augmentation index, remains mechanistically under-researched. Understanding the etiopathogenesis of these changes may hold out the promise of much more efficient maneuvers to cause sustained regression or more effective prevention of LV hypertrophy in dialysis patients.

Reprint requests to Dr. David J.A. Goldsmith, Renal Unit, 4th Floor Thomas Guy House, Guy's Hospital, London SE1 9RT, England, United Kingdom.
E-mail: david.goldsmith@gstt.sthames.nhs.uk

APPENDIX

Abbreviations used in this article are: AGI, augmentation index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AV, arteriovenous; BP, blood pressure; BSA, body surface area; EDD, end-diastolic LV diameter; ESD, end systolic diameter; ESP, end systolic pressure; FSI, fractional shortening index; HD, hemodialysis, IVC, inferior vena cava; IVST, interventricular septal thickness; Kt/V, derived dialysis dose (urea); LA, left atrial diameter; LV, left ventricle; LVM, LV mass; LVMI, LV mass indexed for body surface area; MVCF, mean velocity of circumferential fiber shortening; PWT, posterior wall thickness; PWV, pulse wave velocity.

REFERENCES

1. Raine AEG, Margreiter R, Brunner FP: Report on management of renal failure in Europe, XXII, 1991. *Nephrol Dial Transplant* 7(Suppl 2):7–35, 1992
2. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C: Mortality risk factors in patients treated by chronic hemodialysis: Report of the Diaphane collaborative study. *Nephron* 31:103–110, 1982
3. Luik AJ, Kooman JP, Leunissen KML: Hypertension in haemodialysis patients: Is it only hypervolaemia? *Nephrol Dial Transplant* 12:1557–1560, 1997
4. Goldsmith DJA, Covic A, Venning MC, Ackrill P: Ambulatory blood pressure monitoring in renal dialysis and transplant patients. *Am J Kidney Dis* 29:593–600, 1997
5. Covic A, Goldsmith DJA, Georgescu G, Venning MC, Ackrill P: Echocardiographic findings in long-term, long-hour haemodialysis patients. *Clin Nephrol* 45:104–110, 1996
6. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 49:1379–1385, 1996
7. O'Rourke MF: Mechanical principles in arterial disease. *Hypertension* 26:1–8, 1995
8. O'Rourke MF, Blazek JV, Morreels CL, Krovetz LJ: Pressure wave transmission along the human aorta. *Circ Res* 23:567–579, 1968
9. Stergiopulos N, Westerhof BE, Westerhof N: Physical basis of pressure transfer from periphery to aorta: A model-based study. *Am J Physiol* 274:H1386–H1392, 1998
10. Safar ME, Frohlich ED: The arterial system in hypertension. *Hypertension* 26:10–14, 1995
11. London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F: Cardiac and arterial interactions in end-stage renal disease. *Kidney Int* 50:600–608, 1996
12. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM: Carotid arterial stiffness as a predictor of cardiovascular and all- cause mortality in end-stage renal disease. *Hypertension* 32:570–574, 1998
13. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K, London AM: Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 37:137–142, 1990
14. Blacher J, Demuth K, Guerin AP, Safar ME, Moatti N, London GM: Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 18:535–541, 1998
15. Goldsmith DJA, Covic A, Sambrook P, Ackrill P: Vascular calcification in long-term haemodialysis patients in a single unit: A retrospective analysis. *Nephron* 77:37–43, 1997
16. O'Rourke M: Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension* 15:339–347, 1990
17. London GM, Pannier BM, Guerin AP, Marchais SJ, Safar ME, Cuche J-L: Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease: Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 90:2786–2796, 1994
18. Dahlof B, Pennert K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients: A meta-analysis of 109 treatment studies. *Am J Hypertens* 5:95–110, 1992
19. Shimamoto H, Shimamoto Y: Lisinopril reverses left ventricular hypertrophy through improved aortic compliance. *Hypertension* 28:457–463, 1996
20. Karamanoglu M, Avolio A, O'Rourke M: Real-time estimation of aortic pressure wave contour from non-invasive measurements of the peripheral pulse in the upper limb. *Aust J Cardiol* 10:329–330, 1990
21. Kelly RP, Hayward C, Ganis J, Daley J, Avolio A, O'Rourke MF: Noninvasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. *J Vasc Med Biol* 1:142–149, 1989
22. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ: Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 16:2079–2084, 1998
23. Yaginuma T, Cohn JN: Introduction to wave reflection, wave travel and changes with modification of geometric and physical parameters. *J Hypertension* 10:S71–S72, 1992
24. Chen C-H, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan WL, Kass DA: Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. *Circulation* 95:1827–1836, 1997
25. Cameron JS, Hicks J: Frederick Akbar Mahomed and his role in the description of hypertension at Guy's Hospital. *Kidney Int* 49:1488–1506, 1996
26. London GM: Increased arterial stiffness in end-stage renal failure: Why is it of interest to the clinical nephrologist? *Nephrol Dial Transplant* 9:1709–1712, 1994
27. Asmar RG, Pannier B, Santoni JP, London GM, Levy BI, Safar ME: Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. *Circulation* 78:941–950, 1988
28. London GM, Drueke TB: Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 51:1678–1694, 1997
29. Campese VM: Autonomic nervous system dysfunction in uraemia. *Nephrol Dial Transplant* 5(Suppl 1):98–101, 1990
30. London GM, Safar ME: Autonomic nervous system and large conduit arteries, in *The Arterial System in Hypertension*, edited by

O'Rourke M, Safar ME, Dordrecht, Kluwer Academic, 1993, p 181
31. London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, Froment L: Salt and water retention and calcium blockade in uremia. *Circulation* 82:105–113, 1990
32. Hand MF, Haynes WG, Webb DJ: Hemodialysis and L-arginine, but not D-arginine, correct renal failure-associated endothelial dysfunction. *Kidney Int* 53:1068–1077, 1998
33. Saba PS, Roman MJ, Pini R, Spitzer M, Ganau A, Devereux RB: Relation of arterial pressure waveform to left ventricular and carotid anatomy in normotensive subjects. *J Am Coll Cardiol* 22:1873–1880, 1993